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PATENT SPECIFICATION

NO DRAWINGS

1,189,720

1,189,720

Date of Application and filing Complete Specification: 28 Nov., 1967.
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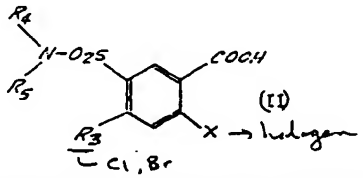
COMPLETE SPECIFICATION

Aromatic Sulfamoyl Compounds

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns compounds of the formula



(I)

in which X stands for halogeno, R_2 stands for a chlorine or a bromine atom, R_4 stands for hydrogen or a residue of aliphatic characteristics, an acyl group, an araliphatic residue or an aliphatic residue substituted by a heterocyclic group of aromatic characteristics and R_5 is an aromatic radical or a heterocyclic group of aromatic characteristics, as well as esters, acid halides, amides, hydrazides or salts of such compounds.

The halogen atom X is particularly a fluorine or chlorine atom.

A residue of aliphatic characteristics is a residue in which the carbon atom bound to the nitrogen atom, to which the residue of aliphatic characteristics is attached, is not part of an aromatic system. Such residue is, for example, an aliphatic radical, such as an aliphatic hydrocarbon radical, and is represented, for example, by lower alkyl, e.g. methyl, ethyl or straight or branched propyl, butyl, pentyl, hexyl or heptyl, such as isopropyl, isobutyl or neopentyl, lower alkenyl, e.g. vinyl, allyl, methallyl, or 2-butenyl, or lower alkynyl, e.g. propargyl.

Another residue of aliphatic characteristics is a cycloaliphatic radical, such radical being of monocyclic or bicyclic nature, for example, a cycloaliphatic hydrocarbon radical, which has preferably from five to seven ring-carbon atoms and which may optionally be substituted by, for example up to four, lower alkyl groups. Such radicals are, for example, cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 2-norbornanyl, 7-norbornanyl, 1-decahydronaphthyl or 2-decahydronaphthyl, or cycloalkenyl, e.g. 1- or 2-cyclopentenyl, 2,4 - cyclopentadienyl, 1-, 2- or 3-cyclohexenyl, 2,5-cyclohexadienyl or 5-norbornen-2-yl; the above cycloalkyl and cycloalkenyl groups may be substituted as indicated, for example, by one, two or three methyl groups.

A further residue of aliphatic characteristics is a cycloaliphatic-aliphatic residue, for example, a cycloaliphatic-aliphatic hydrocarbon residue, in which the aliphatic portion is, for example, lower alkyl, particularly methyl, as well as ethyl or straight or branched propyl or butyl. These aliphatic radicals are substituted in any of the positions available for substitution by the above mentioned cycloaliphatic, for example, cycloaliphatic hydrocarbon residues, such as the cycloalkyl or cycloalkenyl radicals previously mentioned. Thus, cycloaliphatic-aliphatic radicals of this type are cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl residues.

The above residues of aliphatic characteristics may be substituted and/or its carbon atoms may be interrupted by hetero atoms, e.g. an oxygen, a sulfur and/or an optionally substituted, e.g. lower alkyl substituted, nitrogen atom. Substituents are, for example, func-

tional groups, such as free or functionally converted, for example, etherified or esterified hydroxy or mercapto groups, such as halogen, e.g. fluorine, chlorine, or bromine as well as iodine atoms, lower alkoxy, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy or isobutyloxy groups, halogeno-lower alkoxy groups, lower alkyl mercapto, e.g. methylmercapto or ethylmercapto groups, halogeno-lower alkyl-mercapto groups, or hydroxy or mercapto groups esterified by lower alkanoic acids, e.g. acetic, propionic, butyric or pivalic acid, as well as by lower alkenoic acids, e.g. acrylic or methacrylic acid, or by R_c-benzoic, R_c-phenyl-lower alkanoic or R_c-phenyl-lower alkenoic acids, in which R_c stands for hydrogen, lower alkyl, lower alkoxy, lower alkylmercapto, trifluoromethyl, nitro, amino or di-lower alkylamino, e.g. dimethylamino or diethylamino, or halogeno, such as benzoic, phenylacetic or cinnamic acid. Other functional groups substituting a residue of aliphatic characteristics are, for example, free or functionally converted, such as esterified or amidated carboxyl groups, or amino, preferably secondary or tertiary amino groups.

Residues of aliphatic characteristics carrying substituents and/or being interrupted by heteroatoms are, for example, aliphatic residues, such as aliphatic hydrocarbon residues, particularly lower alkyl groups, carrying substituents and/or being interrupted by heteroatoms, such as halogeno-lower alkyl, e.g. 2-chloroethyl, 2-bromoethyl, 3,3-difluoropropyl or 4-chlorobutyl, lower alkoxy-lower alkyl, e.g. 2-ethoxyethyl or 3-methoxypropyl, lower alkyl-mercapto-lower alkyl, e.g. 2-ethylmercaptoethyl, halogeno-lower alkoxy-lower alkyl, e.g. 2 - (2 - chloroethoxy) - ethyl or 2 - (2,2 - dichloroethoxy) - ethyl, halogeno-lower alkyl - mercapto - lower alkyl, e.g. 2 - (2,2,2 - trifluoroethyl - mercapto) - ethyl, carbamoyl-lower alkyl or N,N-di-lower alkyl-carbamoyl-lower alkyl, e.g. carbamoylmethyl, N,N-dimethylcarbamoyl-methyl, 2-carbamoylethyl or 2-N,N-diethylcarbamoyl-ethyl, mono-lower alkyl-amino-lower alkyl, di-lower alkyl-amino-lower alkyl or lower alkyleneamino-lower alkyl, as well as lower oxaalkylene-amino-lower alkyl, lower thiaalkyleneamino-lower alkyl or optionally aza-substituted, for example, aza-lower alkyl-substituted, lower azaalkyleneamino-lower alkyl, in which the oxa, thia or aza portion is separated from the amino grouping by at least two carbon atoms, e.g. 2-ethylaminoethyl, 2-dimethylaminoethyl, 3-diethylaminopropyl, 2-pyrrolidinoethyl, 2 - piperidinoethyl, 2 - (4 - methyl - piperazino) - ethyl or 2-morpholinoethyl.

Other residues of aliphatic characteristics carrying substituents and/or being interrupted by heteroatoms are cycloaliphatic, such as cycloaliphatic hydrocarbon residues, particularly cycloalkyl or cycloalkenyl groups, having preferably 5, 6 or 7 ring-carbon atoms, primarily those interrupted by heteroatoms, above all by an oxygen atoms, as well as optionally substituted, such as by lower alkyl. Such residues are, for example, 5-, 6- or 7-membered mono-oxacycloalkyl or monooxacycloalkenyl, e.g. 2- or 3-tetrahydrofuryl, 2,3-dihydro 2-pyranyl or tetrahydro-2-pyranyl radicals.

Furthermore, radicals of aliphatic characteristics carrying substituents and/or being interrupted by heteroatoms, are also cycloaliphatic-aliphatic, such as cycloaliphatic-aliphatic hydrocarbon radicals, particularly cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl residues, having preferably 5, 6 or 7 ring members, of which one is preferably a heteroatom, above all an oxygen atom, and being optionally substituted, for example, by lower alkyl. Such residues are, for example, mono-oxacycloalkyl-lower alkyl or mono-oxacycloalkenyl-lower alkyl, having preferably 5, 6 or 7 ring-members, e.g. 2-tetrahydrofurfuryl, 2 - methyl - 2 - tetrahydrofurfuryl, 2,3 - dihydro - 2 - pyranylmethyl or 2 - tetrahydropyranyl-methyl.

Heteroatoms present in the above residues of aliphatic characteristics are preferably separated by at least two carbon atoms from the nitrogen atom, to which such residues are attached as substituents.

In an araliphatic residue, the aliphatic portion represents an aliphatic hydrocarbon residue, e.g. lower alkyl or lower alkenyl, which groups have preferably up to four carbon atoms, particularly methyl; together with the aromatic portion,. these residues form primarily aryl-lower alkyl or aryl-lower alkenyl groups, in which the aryl group is of monocyclic or bicyclic nature, such as benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenyl-2-propyl, 4-phenyl-butyl or 2-phenyl-2-butyl, as well as styryl or cinnamyl.

The aryl portion in the above araliphatic residues may optionally be substituted by one or more than one of the same or of different substituents, such as lower alkyl, e.g. as mentioned before, free or functionally converted, e.g. etherified or esterified hydroxy or mercapto, such as lower alkoxy, e.g. as shown above, lower alkylenedioxy, e.g. methylenedioxy, 1,1 - ethylene dioxy, or 1,2 - ethylenedioxy groups, lower alkyl-mercapto, e.g. as mentioned above, or halogeno, e.g. as mentioned above; trifluoromethyl; nitro, primary, secondary or tertiary amino, especially di-lower alkylamino, e.g. as mentioned above, or acylamino, in which acyl is more especially one of the residues of the acids described before, such as lower alkanoyl, as well as lower alkenoyl, but also R_c-benzoyl, R_c-phenyl-lower alkanoyl or R_c-phenyl-lower alkenoyl, in which R_c has the previously given meaning; sulfamoyl; carbamoyl; cyano; or aromatic groups, particularly monocyclic aryl, e.g. phenyl, optionally substituted by the sub-

stituents shown above. Preferred as aromatic portions in araliphatic residues are R_c-phenyl groups, in which R_c has the above given meaning.

An araliphatic radical may also be partially saturated in the aromatic, particularly in a bicyclic or tricyclic aromatic portion and be bound to the nitrogen atom through its saturated aliphatic portion. Such radicals are, for example, 1-indanyl, 2-indanyl, 1,2,3,4-tetrahydro-1-naphthyl, 1,2,3,4 - tetrahydro - 2 - naphthyl or 9-fluorenyl, as well as 2-indolinyl.

In an aliphatic residue substituted by a heterocyclic group of aromatic characteristics, the aliphatic portion represents an aliphatic hydrocarbon residue, e.g. lower alkyl or lower alkenyl, which groups have preferably up to four carbon atoms, particularly methyl. The heterocyclic radicals of aromatic characteristics are of monocyclic, as well as bicyclic nature, and are, especially, monooxacyclic, monothiacyclic or monoazacyclic radicals of aromatic characteristics. Together with the aliphatic portion, they form, for example, monocyclic, as well as bicyclic, monooxacyclic-, meno-thiacyclic- or monoazacyclic-lower alkyl or monocyclic, as well as bicyclic, monooxacyclic-, monothiacyclic- or mono-azacyclic-lower alkenyl groups.

Heterocyclic radicals substituting aliphatic residues may optionally be substituted in the same way as the previously mentioned aromatic groupings of araliphatic residues; they represent, for example, pyridyl, e.g. 2-, 3-, or 4-pyridyl, furyl, e.g. 2- or 3-furyl, or thienyl, e.g. 2- or 3-thienyl groups, but also isooxazolyl, e.g. 5-isooxazolyl, oxazolyl, e.g. 2-oxazolyl, thiazolyl, e.g. 2-thiazonyl, thianaphthyl, e.g. 6-thianaphthenyl or 2,3-dihydro-6-thianaphthenyl, or benzimidazolyl, e.g. 2-benzimidazolyl radicals.

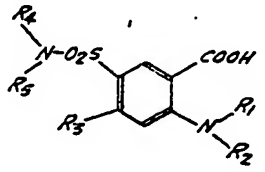
Furthermore, part of a heterocyclic group, especially of polycyclic nature, may be saturated, the group being connected through the saturated portion with aliphatic character, thus representing an aliphatic residue substituted by a heterocyclic radical of aromatic characteristics.

An aromatic radical, representing R_3, stands preferably for a monocyclic or bicyclic aryl group, such as one of those mentioned above, whereas a heterocyclic radical of aromatic characteristics representing R_3 is one of the above monocyclic, as well as bicyclic, particularly monooxacyclic, monothiacyclic or monoazacyclic radicals of aromatic characteristics, such as one of those mentioned above. R_3 stands particularly for an R_c-phenyl group, in which R_c has the previously given meaning.

Acyl derivatives of the comp unds of this invention are preferably those containing acyl radicals of a lower alkanoic, e.g. acetic, propionic, butyric or pivalic acid, but also of a lower alkenoic, e.g. acrylic or methacrylic acid, or of an R_c-benzoic, R_c-phenyl-lower alkanoic or R_c-phenyl-lower alken ic, e.g. benzoic, phenylacetic or cinnamic acid. Acyl derivatives are those of primary, as well as secondary amino groups, but also of free hydroxy or mercapto groups as previously indicated.

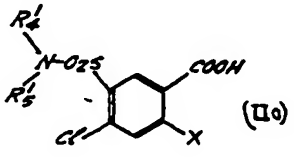
The term "lower", whenever used hereinbefore or below in connection with an organic group, radical or compound, unless otherwise specified, denotes such group, radical or compound as having up to 7, above all up to 4 carbon atoms.

The compounds of the invention are valuable starting materials, for example, for the manufacture of compounds of the formula



in which R_3, R_4 and R_5 have the previously given meaning, each of R_1 and R_2 stands for a residue of aliphatic characteristics, an araliphatic residue or an aliphatic residue substituted by a heterocyclic group of aromatic characteristics and R_2 also represents hydrogen, or R_1 and R_2, when taken together also represent a bivalent residue of aliphatic characteristics, or esters and acyl derivatives thereof, as well as their salts. Compounds of this type, which are described in detail in application No. 54085/67 (Serial No. 1189719) exhibit valuable pharmacological properties. Above all, they show diuretic, natriuretic and chloriuretic activity with rapid onset of action and high urine excretion levels, but low potassium excretion levels. These pharmacological effects can be demonstrated in animal tests using, for example, mammals, e.g. rats or dogs, as test animals. They are, therefore, useful pharmacologically, for example, as test substances in animals, as well as medicinally, particularly as diuretic, natriuretic or chloriuretic agents. Furthermore, the novel compounds of this invention are also useful as intermediates in the preparation of other valuable products, primarily of pharmacologically active compounds.

Particularly useful are the compounds of the formula



(IIa)

in which X has the previously given meaning, R_1' represents hydrogen, lower alkyl, (R_c'-

phenyl)-lower alkyl, in which lower alkyl carrying R_4'-phenyl has from one to four chain-carbon atoms or lower alkanoyl, R_4' stands for hydrogen, lower alkyl, lower alkoxy, lower alkyl-mercapto, halogeno, trifluoromethyl or di-lower alkylamino, and R_4' is an R_4'-phenyl group, a monocyclic R_4''-monooxacyclic group of aromatic characteristics, a monocyclic R_4'' - monothiacyclic group of aromatic characteristics, or a monocyclic R_4'' - monoazocyclic group of aromatic characteristics. R_4'' stands for hydrogen or lower alkyl; lower alkyl esters, R_4'-phenyl-lower alkyl esters, N-unsubstituted or N-lower alkyl-, N-R_4'-phenyl- or N-R_4'-phenyl-lower alkyl-substituted amides or hydrazides and salts, e.g. alkali metal, alkaline earth metal or ammonium salts of such compounds.

Particularly valuable are compounds of the above formula IIa, in which X is fluoro or chloro, R_1' is hydrogen, and R_4' stands for phenyl, as well as compounds of formula IIa, in which X is fluoro or chloro, R_1' is hydrogen or methyl, as well as lower alkanoyl and R_4' stands for phenyl, methyl-phenyl, methoxy-phenyl, fluoro-phenyl, chloro-phenyl, trifluoromethyl-phenyl, nitro-phenyl, aminophenyl, biphenylyl or thianaphthenyl, as well as 2,3-dihydro-thianaphthenyl, and salts, such as alkali metal, alkaline earth metal or ammonium salts of such compounds.

Especially useful are the 4-chloro-5-phenylsulfamoyl-2-X-benzoic acids and the 4-chloro-5 - (4 - methoxy-phenylsulfamoyl) - 2 - X - benzoic acids, in which X is fluoro or chloro.

The compounds of the invention are prepared according to methods in themselves known, for example, by reacting a 2,4-dihalogeno-benzoic acid or a functional derivative thereof with chlorosulfonic acid in order to yield the 5-chlorosulfonyl-2,4-dihalogeno-benzoic acid; the latter or a functional derivative thereof is then reacted with an amine of the formula $R_4—NH—R_5$ in order to obtain the compounds of formula I, in which X stands for halogeno, or a functional derivative thereof. The latter, e.g. esters, acid halides, amides or hydrazides, may also be prepared from the corresponding acids of formula I by conventional methods.

The above process is carried out according to standard methods, in the presence or absence of diluents, preferably those inert to the reagents and capable of dissolving them, and/or of catalysts or condensing agents, and, if necessary, in an inert gas, e.g. nitrogen atmosphere, while cooling or at an elevated temperature, and/or under increased pressure.

The compounds obtained according to the above procedure may be converted into each other according to known methods. For example, resulting compounds, in which R_1 stands for hydrogen, may be reacted with a reactive ester of an alcohol, in which the organic portion corresponds to one of the organic radicals representing R_4 and, for example, a hydrohalic or sulfonic acid. Resulting compounds having a hydroxy group, or a primary or secondary amino group may be acylated, for example, by treatment with a reactive functional derivative if an appropriate acid, such as a halide or anhydride thereof, e.g. thionyl chloride, acetyl chloride or acetic acid anhydride. Resulting acyl derivatives or esters may be hydrolyzed, for example, by treatment with acidic or alkaline hydrolyzing agents, whereas resulting esters may be esterified and resulting acids esterified in a known manner. Any resulting amide or hydrazide may be converted into the free acid, for example, by hydrolysis in the usual manner, for example, by treatment with a base, e.g. an aqueous alkali metal hydroxide or alkaline earth metal hydroxide, as well as a quaternary ammonium hydroxide.

The invention further includes any modification of the process, in which the starting materials are formed under the reaction conditions, or reaction components are used in the form of derivatives thereof, such as their salts. Those starting materials are then used in the process of the invention which lead to the formation of those compounds indicated above as being especially valuable.

The compounds of the invention are obtained in the free form or in the form of their salts, depending on the conditions under which the process is carried out; salts are also included within the scope of the present invention. They are particularly those of resulting free acids with inorganic or organic bases, primarily the alkali metal or alkaline earth metal, e.g. sodium, potassium, magnesium or calcium salts, or the ammonium salts with ammonia or amines, for example, mono-, di- or tri-lower alkylamines, mono-, di- or tri-cycloalkyl-amines, mono-, di- or tri-cycloalkyl-lower alkylamines, mono-, di- or tri-aralkylamines, mixed amines or tertiary nitrogen bases of aromatic characteristics, such as pyridine, collidine or lutidine. Resulting compounds containing basic groupings may also form acid addition salts, such as those with inorganic acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric, nitric or perchloric acid, or with organic acids, for example, ascorbic acid and aliphatic or aromatic carboxylic or sulfonic acids, e.g. formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, maleic, hydroxymaleic, pyroracemic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxy-benzoic, salicylic, 4-aminosalicylic, embonic, nicotinic, methanesulfonic, ethane sulfonic, hydroxyethane sulfonic, ethylene sulfonic, halogeno-benzene sulfonic, toluene sulfonic, naphthalene sulfonic, sulfanilic, r N-cyclohexyl-sulfamic acid.

The following Examples illustrate the invention and are not t be construed as being

limitations thereof. Temperatures are given in degrees Centigrade.

EXAMPLE 1

A mixture of 5.8 g of 5-chlorosulfonyl-2,4-dichlorobenzoic acid, 7.5 g of aniline, and 50 ml of ethyl acetate is stirred for 4 hours at room temperature, then filtered; the residue is washed with ethyl acetate and the filtrate is evaporated under reduced pressure. The residue is triturated with 2N hydrochloric acid, the aqueous solution is decanted off and the precipitate is taken up in 100 ml of a 10% aqueous potassium carbonate solution, which is filtered to yield residue A. The filtrate is extracted with ether and the aqueous layer is acidified with hydrochloric acid. The precipitate formed is filtered off, washed with water and recrystallized from aqueous ethanol to yield the 2,4 - dichloro - 5 - phenylsulfamoylbenzoic acid, melting point 211—213°. Residue A is also recrystallised from aqueous ethanol to yield the 2,4-dichloro-5-phenylsulfamoyl-benzoic acid N-phenylamide, melting point 173—175°.

The starting material is prepared as follows: At room temperature 50 g of 2,4-dichloro-benzoic acid are added portionwise to 250 g of chlorosulfonic acid while stirring. The resulting solution is heated to about 180°, stirred for 3 hours, then cooled to room temperature and poured into ice. The aqueous mixture is filtered, the filter residue washed with water and dissolved in 400 ml of ethyl acetate. The solution is dried, filtered and evaporated: the residue is triturated with hexane to yield the 5-chlorosulfonyl-2,4-dichloro-benzoic acid.

EXAMPLE 2

To a solution of 5.8 g of 2,4-dichloro-5-chlorosulfonyl-benzoic acid in 50 ml of ethyl acetate is added while stirring 8.6 g of p-toluidine, followed by 100 ml of ethyl acetate. The mixture is stirred at room temperature for 2 hours, refluxed for 2 hours while stirring, then cooled and filtered. The filter residue is washed with ethyl acetate and the filtrate is evaporated under reduced pressure. The residue is treated with 10 ml of concentrated hydrochloric acid and extracted with ethyl acetate; the organic layer is separated and extracted with a 10% aqueous potassium carbonate solution. The aqueous solution is acidified with hydrochloric acid, and the resulting precipitate is filtered off, washed with water and recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-(4-methyl-phenyl-sulfamoyl)-benzoic acid, melting point 202—204°.

According to the procedure previously illustrated, the following compounds are obtained by using equivalents amounts of the appropriate starting materials:

2,4 - dichloro - 5 - (4 - methoxy - phenyl - sulfamoyl) - benzoic acid, melting point at 224—226° after recrystallization from methanol;

2,4 - dichloro - 5 - (4 - fluorophenyl - sulfamoyl) - benzoic acid, melting point 231—233° after recrystallization from ethanol;

2,4 - dichloro - 5 - (2 - chloro - phenyl - sulfamoyl) - benzoic acid, melting point 168—170° after recrystallization from ethanol;

2,4 - dichloro - 5 - (3 - chloro-phenyl - sulfamoyl) - benzoic acid, melting point 190—192° after recrystallization from ethanol;

2,4 - dichloro - 5 - (4 - chloro - phenyl - sulfamoyl) benzoic acid, melting point 238—240° after recrystallization from ethanol;

2,4 - dichloro - 5 - (3 - trifluoromethyl - phenyl - sulfamoyl) - benzoic acid, melting point 214—216° after recrystallization from ethanol;

2,4 - dichloro - 5 - (4 - trifluoromethyl - phenyl - sulfamoyl) - benzoic acid, melting point 238—239° after recrystallization from ethanol;

2,4 - dichloro - 5 - (4 - nitro-phenyl - sulfamoyl) - benzoic acid, melting point 269—271° after recrystallization from ethanol; and

5 - (2 - biphenyl - sulfamoyl) - 2,4 - dichloro - benzoic acid, melting point 175—176° after recrystallization from ethanol.

EXAMPLE 3

To a solution of 5.8 g of 5 - chlorosulfonyl - 2,4 - dichloro-benzoic acid in 50 ml of ethyl acetate is added 12 g of 4-amino-acetanilide, followed by 50 ml of ethyl acetate. The mixture is stirred for 2 hours at room temperature and refluxed for 2 hours while stirring, then cooled to room temperature and filtered. The residue (A) is washed with ethyl acetate; the filtrate is evaporated under reduced pressure and the residue (B) is triturated with water and 10 ml of concentrated hydrochloric acid, then filtered off, washed with water and dried. The combined residues (A) and (B) are dissolved in 60 ml of a 10% aqueous potassium carbonate solution, the solution is washed with ether and acidified with hydrochloric acid. The precipitate formed is filtered off and washed with water to yield the 5 - (4 - acetylamino - phenylsulfamoyl) - 2,4 - dichlorobenzoic acid, melting point about 150°.

EXAMPLE 4

The mixture of 7.1 g of 5 - (4 - acetylamino-phenyl - sulfamoyl) - 2,4 - dichlorobenzoic acid and 60 ml of 2N aqueous sodium hydroxide solution is refluxed for 90 minutes. After cooling to room temperature, it is acidified with concentrated hydrochloric acid, the resulting precipitate is filtered off, the residue is taken up in ethanol, the solution is filtered and evaporated under reduced pressure to yield the 5-(4-amino-phenyl-sulfamoyl) 2,4 -

dichloro-benzoic acid hydrochloride, melting point 185 (decomposition).

EXAMPLE 5

A mixture of 150 g of 2,4-dichloro-benzoic acid and 660 g of chlorosulfonic acid is heated to 150—155° for 3 hours while stirring. A total of 223 g of chlorosulfonic acid is then distilled off under reduced pressure and the cold residue is poured into a mixture of 1650 g of ice and 125 ml of water. The resulting precipitate is filtered off, washed with cold water and dissolved in 800 ml of ethyl acetate. The solution is dried and filtered, the filtrate is diluted with 600 ml of ethyl acetate and the solution containing the 2,4-dichloro - 5 - chlorosulfonyl - benzoic acid is cooled in a water bath. A mixture of 216 g of aniline and 220 ml of ethyl acetate is added at such a rate that the temperature remains below 30° The reaction mixture is then stirred for 4 hours at 25—30°, then 4 g of charcoal are added. After filtration and washing the filter residue with 125 ml of ethyl acetate, the solution is washed first with 450 ml of 3N hydrochloric acid, then with 550 ml of water, and finally extracted with 700 ml of 7% aqueous sodium carbonate solution. The aqueous basic extract is separated and carefully acidified with concentrated hydrochloric acid; the precipitate formed is filtered off and dried at 75° C under reduced pressure to yield the 2,4 - dichloro - 5 - phenyl - sulfamoyl - benzoic acid, melting point 212—216°.

EXAMPLE 6

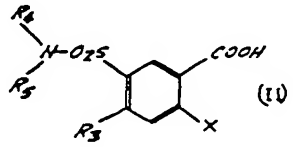
To a solution of 1.9 g of 6-amino - 2,3 - dihydro - thianaphthene in 25 ml of ethyl acetate and 3 ml of pyridine are added slowly while stirring, 2.9 g of 5-chlorosulfonyl - 2,4 - dichloro - benzoic acid. The mixture is stirred for 3 hours at room temperature and allowed to stand for 16 hours, then made strongly acidic with hydrochloric acid and extracted with ethyl acetate. The organic extract is washed with water, dried and evaporated under reduced pressure. The residue is taken up in a 1N aqueous sodium hydroxide solution, the solution is filtered and the filtrate is acidified. The precipitate formed is filtered off and recrystallized first from aqueous ethanol, then from methanol to yield the 2,4 - dichloro - 5 - (2,3 - dihydro - 6 - thianaphthenyl - sulfamoyl) - benzoic acid.

EXAMPLE 7

To a solution of 11.6 g of 5-chlorosulfonyl-2,4-dichloro-benzoic acid in 100 ml of ethyl acetate are added slowly 17.1 g of N-methyl-aniline; the mixture is stirred at room temperature for 4 hours, then filtered. The filtrate is evaporated under reduced pressure and the residue is taken up in water and 20 ml of concentrated hydrochloric acid. The mixture is extracted with ethyl acetate, the organic extract is washed with water and shaken with a 10% aqueous potassium carbonate solution. The aqueous layer is separated and acidified with concentrated hydrochloric acid; the precipitate formed is filtered off and recrystallized from aqueous ethanol to yield the 2,4-dichloro - (N - methyl - N - phenyl - sulfamoyl) - benzoic acid, m.p. 170—171°.

WHAT WE CLAIM IS:—

1. Compounds of the formula



(I)

in which X stands for halogeno, R_3 stands for a chlorine or a bromine atom, R_4 stands for hydrogen, a residue of aliphatic characteristics, an acyl group, an araliphatic residue or an aliphatic residue substituted by a heterocyclic group of aromatic characteristics, and R_5 is an aromatic radical or a heterocyclic group of aromatic characteristics.

2. Esters, acid halides, amides, hydrazides or salts of the compounds of claim 1.

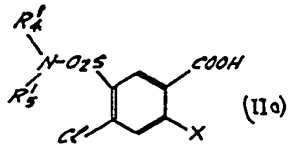
3. The compounds of any one of claims 1 and 2, in which X stands for fluoro or chloro.

4. The compounds of the formula II according to claim 1, wherein X stands for halogeno, R_3 and R_5 have the meaning given in claim 1 and R_4 stands for hydrogen.

5. Esters, acid halides, amides, hydrazides or salts of the compounds of claim 4.

6. The compounds of claims 4 and 5, in which X is fluoro or chloro.

7. The compounds of the formula



(IIa)

in which X is halogeno, R_4' represents hydrogen, lower alkyl, (R_6'-phenyl)-lower alkyl, in which lower alkyl carrying R_6'-phenyl has from one to four chain-carbon atoms, or lower alkanoyl and R_5' is an R_6'-phenyl group, a mono-cyclic R_6''-monooxacyclic group of aromatic characteristics, a monocyclic R_6''-monothiacyclic group of aromatic characteristics, or a monocyclic R_6''-monoazacyclic group of aromatic characteristics, R_6' standing for hydrogen, lower alkyl, lower alkoxy, lower alkyl-mercapt , halogen , trifluoromethyl or di-lower alkylamin and R_6'' for hydrogen or l wer alkyl.

8. Lower alkyl esters, R_6'-phenyl-lower alkyl esters, in which R_6' has the meaning

given in claim 7, N-unsubstituted or N-lower alkyl-, N-R_6'-phenyl- or N-R_6'-phenyl-lower alkyl-substituted amides or hydrazides, or salts of the compounds of claim 7.

9. Compounds of any one of claims 7 and 8, in which X stands for fluoro or chloro.

10. Compounds of the formula IIa according to claim 7, wherein X is halogeno, R_1' is hydrogen, and R_2' is an R_6'-phenyl group, a monocyclic R_6''-monooxacyclic group of aromatic characteristics, a monocyclic R_6''-monothiacyclic group of aromatic characteristics, or a monocyclic R_6''-monoazacyclic group of aromatic characteristics, R_6' standing for hydrogen, lower alkyl, lower alkoxy, lower alkylmercapto, halogeno, trifluoromethyl or di-lower alkylamino and R_6'' for hydrogen or lower alkyl.

11. Lower alkyl esters, R_6'-phenyl-lower alkyl esters, in which R_6' has the meaning given in claim 10, N-unsubstituted or N-lower alkyl-, N-R_6'-phenyl- or N-R_6'-phenyl-lower alkyl-substituted amides or hydrazides or salts of the compounds of claim 10.

12. Compounds of either one of claims 10 and 11, in which X is fluoro or chloro.

13. Compounds of the formula IIa according to claim 7, in which X is halogeno, R_1' is hydrogen, methyl or lower alkanoyl, and R_2' is phenyl, methyl-phenyl, methoxy-phenyl, fluoro-phenyl, chlorophenyl, trifluoromethyl-phenyl, nitrophenyl, aminophenyl, biphenylyl or thianaphthenyl.

14. Compounds according to claim 13, in which X is fluoro or chloro.

15. 4 - chloro - 5 - phenyl - sulfamoyl - 2 - X - benzoic acids, in which X is halogeno.

16. The compounds of claim 15, in which X is fluoro or chloro.

17. 2,4 - dichloro - 5 - phenylsulfamoyl - benzoic acid.

18. 2,4 - dichloro - 5 - (4 - methoxyphenyl-sulfamoyl) - benzoic acid.

19. Process for the manufacture of compounds as claimed in any one of claims 1—3, 7—9, 13—15 and 18 as described hereinbefore.

20. Process for the manufacture of compounds as claimed in any one of claims 4—6, 10—12, 16 and 17 as described hereinbefore.

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